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STRUCTURE OF NEOOXAZOLOMYCIN, AN ANTITUMOR ANTIBIOTIC

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Summary: Based on the spectroscopic analysis and correlation with the degradation products of oxazolomycin, the structure of neooxazolomycin has been elucidated.

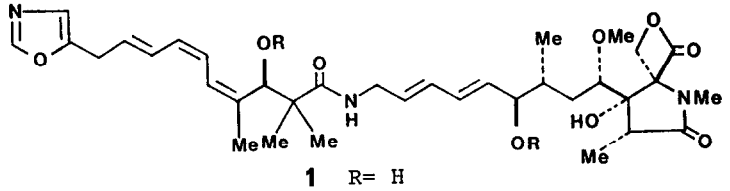
In the preceding report,[1] we described the structure of oxazolomycin (**1**), the antitumor antibiotic. Our interests concerning the structure-activity relationship of **1** were focused on the structure of a conjenar, neooxazolomycin which also exhibited comparable activity against Ehrlich ascites tumor in vivo. We report below the structural elucidation of neooxazolomycin (**2**).

Neooxazolomycin, $C_{34}H_{47}N_3O_9$ [FDMS, m/Z 664 $(M+Na)^+$] contains the triene and diene chromophores, UV (MeOH) 230, 265, 275 and 285 nm like oxazolomycin. However, its IR spectrum revealed the presence of γ-lactone (1765 cm^{-1}) instead of β-lactone in **1**. Then acetylation of neooxazolomycin with Ac_2O and pyridine afforded a triacetate **3**: ^{1}H-NMR (360 MHz, $CDCl_3$) Table 1. Comparison between the ^{1}H-NMR spectra of **3** and the diacetate **4** of oxazolomycin led us to the planar structure and furthermore, the following degradation and chemical transformation confirmed the complete structure **2**, including its absolute configuration.

Triacetate **3** was oxidized with O_3 at -40°C and then reduced with $NaBH_4$. The resulting alcohols were acetylated with Ac_2O and pyridine to give compounds **5** and **6**.[2] The triacetate **5** was consistent with the authentic **5**[1] in the spectral data and optical rotation; the degraded **5**: $[\alpha]_D$= +8.6°(c 0.38, $CHCl_3$).[1] On the other hand, **6** was correlated with the degradation product **7**[1] of **1**. The methyl ester **7** was treated with BBr_3[3] in CH_2Cl_2 at -40°C, followed by treatment with methanol at room temperature. The reaction mixture obtained was acetylated with Ac_2O and pyridine, furnished compound **6** which was found to be identical with **6** degraded from **2** in all spectral data and optical rotation; **6** from **2**: $[\alpha]_D$= +7° (c 7.0, $CHCl_3$), **6** from **1**: $[\alpha]_D$= +5° (c 1.0, $CHCl_3$). Moreover, similarly in the case of **1**, ozonolysis of neooxazolomycin itself (i. O_3 in MeOH, ii. $NaBH_4$, iii. Ac_2O/py) gave compound **8**. This result was consistent with Z-configuration of C4' double bond.

Although the structure of neooxazolomycin (**2**) has been fully determined as described, it is of interest that in spite of the presence of β-lactone in **2**

comparable activity retains. Therefore, we concluded that β-lactone in **1** was not so serious for revelation of activity. Since 5-substituted oxazoles exhibited in vitro cytotoxicity on L-1210 cells,[4] we are examining further structure-activity relationship of **1**, especially around the oxazole ring.



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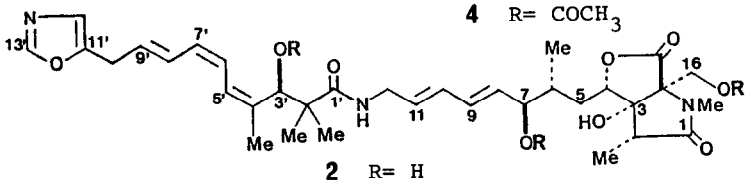
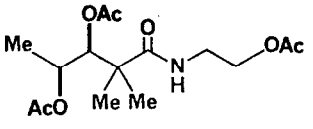
4 R= $COCH_3$



2 R= H

3 R= $COCH_3$



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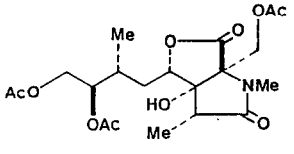

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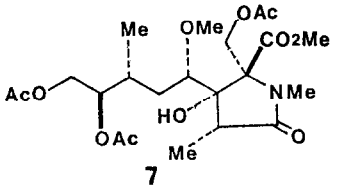

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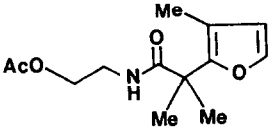

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Table 1. ^{1}H-NMR Signals for Triacetate **3**

Assignment	δ, multi	J, Hz	Assignment	δ, multi	J, Hz
6-Me	1.03 d(3)	6.8	H7	5.20[a] dd(1)	6.9, 4.7
2'-Me	1.21 s(3)		H8	5.56 dd(1)	6.9, 14.4
2'-Me	1.23 s(3)		H11	5.67 dt(1)	6.3, 14.7
2-Me	1.27 d(3)	7.8	H9'	5.79 dt(1)	7.2, 15.0
H5	1.63 m(1)		H3'	5.86[b] s(1)	
4'-Me	1.79 br.s(3)		H7'	5.99 dd(1)	11.8, 11.8
H5, H6	1.8-2.2 m(2)		NH, H9, H10	6.0-6.3 m(3)	
$COCH_3$	2.08 s(9)		H6'	6.35 dd(1)	11.8, 11.8
H2	2.43 q(1)	7.8	H5'	6.48 br.d(1)	11.8
NMe	2.85 s(3)		H8'	6.63 dd(1)	11.8, 15.0
H10'	3.52 br.d(2)	7.2	H12'	6.80 br.s(1)	
H12	3.88 m(2)		H13'	7.81 s(1)	
H16	4.23 d(1)	12.5			
H4	4.31 dd(1)	4.4, 8.6			
H16	4.69 d(1)	12.5			

a. δ 4.32 in **2**, b. δ4.81 in **2**.

REFERENCES AND NOTES

1) The preceding paper in this issue.

2) **6**, $C_{20}H_{29}NO_{10}$: IR ($CHCl_3$) 3450, 1770, 1740, 1695 cm^{-1}; ^{1}H-NMR (90MHz, $CDCl_3$) 1.08 (3H,d,J=7Hz), 1.27(3H,d,J=7Hz), 2.08(3H,s), 2.10(6H,s), 2.10(1H,q,J=7 Hz), 2.88(3H,s), 4.0-4.4(3H,m), 4.20(1H,d,J=12Hz), 4.71(1H,d,J=12Hz), 5.00(1H,m).

3) This reaction was also achieved with BCl_3 in CH_2Cl_2.

4) Data concerning activity of several 5-substituted oxazoles will be published in future.

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